REMARKS

Claims 1-10 and 15-24 were pending and rejected.

Identical amendments are being made in claims 1 and 2, and in accordance with these amendments, dependent claims 4, 5, and 17-21 amended. Those amendments are voluntary and are discussed in Section I, below.

Additional amendments are made in claims 9 and 24 to make them compliant with § 112, 2nd paragraph

The amendments and new claims are supported in the specification as well as in the original claims. In particular, support is found in para [0023] of the published U.S. application.

None of these amendments introduces new matter, nor do they raise new issues that would require further consideration and/or search. Therefore entry of the amended claims after "Final Rejection" is respectfully respected as is their examination at this stage and their allowance.

Withdrawal of Objections and Rejections

Applicants thanks the Examine for the withdrawal of most f the rejections based on Applicant's previous amendments and response.

I. DISCUSSION OF CERTAIN AMENDMENTS

Applicant has made certain amendments in independent claims 1 and 2. The claimed method is "for the integration of physical and genetic maps by associating a restriction fragment, preferably an AFLP fragment with a genetic marker" and provides

> a library of clones containing inserts of the (part of) genome of interest, pooling the clones into pools and fingerprinting the pools using AFLP primer-pairs of higher selectivity, individually fingerprinting the clones in a library using AFLP primer pairs of lower selectivity.

Specification at para. 0023 (of published U.S. application).

The previous (examined) claims recited that K, L, M and N, representing the number of selective nucleotides in AFLP primers" are integers with a value from 0 to 10," and further, that "(K+L) > (M+N)".. Applicant believes that the amendments made to this language would more particularly point out and distinctly claim the subject matter which he regards as his invention. The terminology, K+L (used for the pool) can be less selective than M+N (used for individual clones) even though their sum is higher than M+N. For example, in the case of a +0/+7 (K/L) primer combination vs. a +3/+3 (M/N) primer combination). The sum of the two does not determine the selectivity, but rather the least selective primer seems to do so. So Applicants are

replacing this language with that based on the specification that as quoted above. The new claims read

> *...wherein the forward and reverse AFLP primers used in steps (b) and (e) are of higher selectivity, and the forward and reverse AFLP primers used in step (g) are of lower selectivity*

In keeping with this, dependent claim 4 reads:

> *The method according to claim 1, wherein the AFLP primers used in steps (b) and (e) have in total at least 2 more selective nucleotides than the AFLP primers used in step (g).*

Other dependent claims are similarly amended (with no further discussion here).

II. REJECTIONS UNDER 35 USC § 112, Second Paragraph (INDEFINITENESS)

Claims 7-10, 17-18, and 24, are rejected as being indefinite. Claims 8-10 and 24 are rejected for being dependent from claim 7, directly or indirectly, and thus also comprising the indefinite limitation. The limitation in clam 7 is allegedly confusing because it is unclear what is meant by a "pooling step," and it also it lacks antecedent basis as there appears no "pooling step" in claim 6 or the claims from which it depends.

Applicant's Response

Claim 1(d) has been amended to read as follows

(d) pooling individual clones in the library to generate a multitude of pools, each pool containing a multitude of individual clones from the library;

(Claim 2(c) was similarly amended for consistency.)

There is now an antecedent basis for claim 7 *et seq.*

In claim 9, the language "wherein the contigs are aligned using a computer program suitable for such aligning" lacks antecedent basis as there appears no step of aligning contigs in claim 8 or in any of the claims claim 8 depends.

Applicant's Response

Claim 1(h) has been amended to read as follows:

(h) aligning the individual clone identified in step (g) to generate a contig

(Claim 2(g) was similarly amended for consistency.)

Claim 9 has been amended to read;

> *The method according to claim 8, wherein the contigs are generated using a computer program suitable for said aligning.*

As a result, there exists an antecedent basis for the language claim 9.

Claims 17 and 18 are indefinite due to the language "at least at least.."

Applicant's Response

The typographical error of stating "at least at least" in claims 17 and 18 are moot in view of the amendments to these claims.

Claim 24 recites the method of claim 8, "wherein the computer program is FPC." The limitation lacks antecedent basis

Applicant's Response

Claim 24 is amended by changing the dependency, providing a proper antecedent basis.

In view off the foregoing, the § 112, 2nnd paragraph rejections are moot and may be withdrawn.

III. REJECTION UNDER 35 U.S.C. § 103

Claims 1-10 and 15-24 were rejected under 35 U.S.C. 103(a) as being obvious over Klein *et al.* (Genome Research, 10:789-807, 2000). **("Klein")**

The claims are amended to be drawn to a method for providing an integrated genetic and physical map of a genome or a part thereof, the method comprising the steps of claim 1, which applicants will not repeat here

As stated in the previous Office Action, **Klein** allegedly discloses a method for using AFLP fingerprinting to link genetic markers with physical markers to generate a physical map. The method comprises providing a plurality of genetic markers including markers characterized as AFLP fragments; providing a BAC library of clones and generating a multitude of pools thereof; generating AFLP fingerprint for the pools and the clones thereof; identifying the pools and the clone containing the AFLP fragments characterizing the AFLP fragments, and generating a contig comprising the individual clones corresponding to the individual AFLP markers, wherein the forward and reverse AFLP primers used for AFLP-fingerprinting the pools and the clones are +3/+3 unique primer combinations. See at least Figs. 2-6 and pages 793, and "Methods" on pages 802- 806. The steps of the method are repeated for different markers.

Applicants' prior Response (3/17/10) showed a difference between **Klein** and the instant invention in that **Klein** does not use primers in steps (b) and (e), *i.e.*, fingerprinting of individual clones, which are longer than the primers in step (g), *i.e.* the fingerprinting of the clones from the library. Instead, the primers used by **Klein** are of the same length.

The Action alleges that **Klein** explicitly discloses that its method "resulted in a low but significant error rate," (see page 801, right col.). As interpreted by the Office, this would

"invite[ing]changes and/or modifications of their method." Allegedly, realizing that primers with shorter selective nucleotides have lower selectivity and/or stringency, **Klein** used shorter selective primers in the pre-amplification process (pg 803, left col.).

The Office contends that it would have been well known in the art that a principle of AFLP fingerprinting is that the more selective the nucleotides in the primers, the higher their selectivity. On the other hand, because of higher selectivity, screening a library with them would have higher stringency.

As a consequence, the Office continues, some clones in some pools would not be picked up by such high stringency, which might be one of the reasons that caused the "low but significant error rate" of **Klein's** method. It would therefore have been obvious to modify the **Klein** method to use shorter primers, *i.e.,* fewer selective nucleotides, for fingerprinting the clones from the library in an attempt to lower the stringency and also the error rate.

Given that **Klein** used a large number of primer combinations (see, at least,, page 801, left col.), it would also have been obvious to try different combinations with different numbers of selective nucleotides for fingerprinting the individual clones and for screening the library (such as with a difference of at least 1, or 2 or 3) to obtain the optimal combination that would result in the lowest error rate.

Klein also discloses using the FPC computer program for the AFLP analysis (pg 792). **Klein** also discloses using 4-5x genome equivalents and additional poolings (pg 793). Because **Klein** used 4-5 x genome equivalents for pooling and generated 184 pools in total (pg. 800, left col.), it would he been apparent to one off ordinary skill in the art that each pool would be around 0.02 genome equivalent, which is "not more than the 0.3" or 0.4 or 0.5 genome equivalents as recited in the instant claims.

Applicant's Response

Applicant notes again that certain amendments are being made in claims 1 and 2, and in accordance with these amendments, dependent claims 4, 5, and 17-21. These claims are believed to be even less broad in scope even more distinct from the cited art.

he Action suggests that the statement "*...resulted in a low but significant error rate*" in **Klein** (page 801, right col, first full para) should be enough for a person skilled in the art to arrive at the current invention using this reference alone

One should consider that **Klein** used two methods to order the clones into physical contigs: restriction digest fingerprinting of all clones and AFLP analysis using +3/+3 primer combinations of pools to generate AFLP fingerprints of the clones.

Restriction digest fingerprinting is a very laborious method, but is required due to the high false positive rate (15%) f the AFLP fingerprinting of pools (**Klein**, pg. 796, left col. bottom of 2nd full para). **Klein** solved this problem of false positives mentioned at pg 801, right col.) by combining the two methods described (page 801, right col., first full para 2nd sentence):

> ...To reduce this source of error, BACs were incorporated into the sorghum physical map only when their order or location was verified by two different analyses".

Thus, **Klein** did not suggest or invite the skilled artisan to change or modify their method, but rather provided a solution to this "self-described" problem.

With that in mind, it appears that the Office's position is rooted in hindsight, and the language of the Action states that "it would also have been *obvious to try* different combinations." Although this standard is no longer absolutely prohibited following the Supreme Court 's *KSR* decision (*KSR International Co. v Teleflex, Inc.* 127 Ct, 11727, 82 USPPQ2d, 1385 U.S. 2007) the overall "TSM" test (teaching-suggestion-motivation) was not entirely swept away. The "obvious to try' standard, has long been frowned upon by Federal Circuit and (its predecessor court) C.C.P.A. law. See, *e.g.*, I*n re Tomlinson* 150 USPQ 623,26 (1966); *In re Lemin* 150 USPQ 546,49 (1966); *In re Dien* 152 USPQ 550,552 (1967); *In re Antonie*, 195 USPQ 6,8 (1977); *In re Goodwin*, 198 USPQ 1,3 (1978); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 91 (Fed. Cir. 1986); *Alco Standard Corp. v. Tennessee Valley Authority*, 1 USPQ2d 1337, 1343 (Fed. Cir. 1986), *cert. denied*, 108 S.Ct. 26 (1987; *In re Geiger*, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987); *In re Eli Lilly & Co.* 14 USPQ2d 1741, 1743 (Fed. Cir. 1990).

Notwithstanding the debate over how the concepts/words "infinite" vs. "finite" (with respect to alternatives available to the skilled artisan) should be considered, it is fair to conclude under *KSR* that the Federal Circuit in *In re O'Farrell* (853 F.2d, 84, 903, 7 USPQ2d 17,673 (Fed Cir. 1988) correctly suggested that an invention would not be obvious if the practitioner was faced with "numerous possible choices" without any direction as to which was likely to be successful. Moreover, the "problem/solution analysis favored by (for example) the European Patent Office, although not a staple of U.S. practices was subjected to Supreme Court discussion in *KSR* in a way that could be considered favorable to the application of such reasoning in obviousness analyses.

Even if, *arguendo*, the problem of a "low but significant error rate" posed in **Klein** begged for changes and/or modifications of the **Klein** method (which it does <u>not</u> because **Klein** found a solution that was unlike that of the present invention), the skilled artisan could have selected any of "numerous possible parameters" to change. The following is a list of just a few:

(a) different restriction sites (b) selection of restriction sites that have recognition sites comprising varying number of nucleotides, (c) a different pooling strategy (d) the choice of specific selective bases added to each AFLP primer, (e) the choice of (BAC) library, (f) the PCR conditions, and the like.

The skilled artisan was not put in a position of merely choosing the solution provided by the present invention from a finite number of identified, predictable methods which carried a reasonable expectation of success. Rather, the skilled artisan could have selected from among a set of numerous possible ways in which to decrease the error rate, none of which would have been favored over any of the others as providing a reasonable expectation of success. Given these circumstances, the methods provided by Applicants could not properly be considered obvious over **Klein**, even in "post-KSR" analysis.

For the foregoing reasons, it would be proper to withdraw the § 103 rejection and allow the claims.

IV. CONCLUSION

In conclusion, it is respectfully requested that the above amendments, remarks and requests be considered and entered. Applicant respectfully submits that all the present claims are novel over the cited art and therefore in condition for (further examination and) allowance, and respectfully requests early notice of such favorable action.

Respectfully submitted,
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